

## **The Utility of Clinical Sequencing in the Diagnosis and Treatment of Soft Tissue Sarcomas; Real-World Database on Nationwide Database**

Eiji Nakata, Tomohiro Fujiwara<sup>1</sup>, Toshiyuki Kunisada<sup>2</sup>, Toshifumi Ozaki<sup>3</sup>

<sup>1</sup>Okayama University Hospital, <sup>2</sup>Orthopaedic Surgery, Okayama University, <sup>3</sup>Okayama Univ Hosp/Dept of Ortho Surg

### **INTRODUCTION:**

Soft tissue sarcomas (STS) are rare and heterogeneous tumors arising from mesenchymal connective tissue, accounting for approximately 1%–2% of all malignancies. Due to their rarity and heterogeneity, it is challenging for accurate diagnosis, prognosis, and treatment of sarcoma. Even among expert sarcoma pathologists, diagnostic errors in sarcoma are common, with rates up to 25%. The effective targeted therapies are limited for most sarcomas as the mutational landscape is less studied compared with other malignancies. Recently, next-generation sequencing (NGS)-based comprehensive cancer genome profiling (CGP) has increasingly become a routine practice for patients with solid cancers worldwide. In Japan, the Ministry of Health, Labor, and Welfare designated 11 core hospitals and 100 liaison hospitals in 2018 and expanded designation to 13 core, 32 hub, and 203 liaison hospitals by April 2023 to promote cancer genomic medicine. Since June 2019, three CGP tests - the OncoGuide NCC Oncopanel System (NCC Oncopanel), FoundationOne CDx cancer genome profiling (F1CDx), and FoundationOne Liquid CDx cancer genome profiling have been used under the national health insurance system. To collect genomic information and clinical characteristics of patients who underwent CGP, the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) has also been established since 2018. C-CAT functions as the central database for cancer genomic medicine and assists in decision making by providing reports with information about clinical trials matching patients' genomic data. Almost all the clinical and genomic data of patients who received CGP tests the had been collected in C-CAT. C-CAT has been designing open and responsible for data sharing. Researchers and pharmaceutical companies will be able to access clinical and genomic data deposited in C-CAT after approval of their application by an independent access review committee. Here, we examined the utility of CGP test in the diagnosis and treatment of STS using this nationwide database.

### **METHODS:**

We retrospectively evaluated the records of patients with STS who received F1CDx between November 2019 and May 2022 and registered in C-CAT. We excluded patients with diagnosis of other malignancy. We also excluded patients who received other CGP tests. F1CDx is one of the comprehensive companion diagnostic for all solid tumors approved by the Ministry of Health, Labor, and Welfare in Japan. This assay carries 324 genes and determines nucleotide substitutions, insertions/deletions, and copy number (CN) alterations of 309 genes, fusions of 36 genes, tumor mutation burden (TMB), and microsatellite instability (MSI). High TMB (TMB<sub>H</sub>) was defined as a TMB value >10 muts/Mb. Ranges of the MSI score were assigned MSI-High (MSI-H) or microsatellite stable (MSS).

**RESULTS:** From 2019 to 2022, 1,390 patients with STS were registered in C-CAT. The histological types included leiomyosarcoma in 357 patients, dedifferentiated liposarcoma in 178 patients, and undifferentiated pleomorphic sarcoma in 82 patients, and the others. The most commonly altered genes included TP53, CDKN2A, Rb1, and CDKN2B. Among the 1,390 cases, we observed 110 fusion events in 108 cases (7.7%), and 2 cases showed 2 types of fusion transcripts. Fifteen (2.8%) patients were reclassified based on the detection of highly histology-specific translocations. Among them, an initial diagnosis of sarcoma NOS was classified as Ewing Sarcoma (EWSR1-FLI1 in 2 patients), NTRK-rearranged spindle cell neoplasm (NTRK fusion in 3 patients), CIC-rearranged sarcoma (CIC-DUX4 in 3 patients), and sarcoma with BCOR genetic alterations (BCOR-ZC3H7B in 1 patient) as these gene fusions were identified. We identified potentially actionable kinase fusions in 1.5% of STS, including ALK, BRAF, NTRK1–3, and ROS1 kinase fusions. Among them, 5 patients received genotype-matched therapy and complete response and partial response were achieved in 1 and 3 patients, respectively. TMB<sub>H</sub> was observed in 27 patients (1.9%), including 6 with angiosarcoma, 6 with leiomyosarcoma, and others. Microsatellite instability (MSI High) was observed in 7 patients. Druggable gene alterations were detected in 347 patients (25%) and 55 patients (4%) who received genotype-matched therapy. In 38 patients for whom the effect of treatment could be evaluated, complete response and partial response were achieved in 2 (5%) and 10 (26%) patients, respectively.

**DISCUSSION AND CONCLUSION:** Gounder showed that CGP could lead to refinement or reassignment of 10.5% of diagnoses and 32% of the patients harbored potentially actionable alterations. In this study, 2.8% of patients were reclassified and the actionable gene mutations were found in 25% of the patients with sarcoma by the CGP. Although few patients could receive genotype-matched therapy, they could achieve relatively good control. In conclusion, the comprehensive genomic profiling test appears to be an important tool in the diagnosis and treatment of sarcomas.

Figure1. The frequency of the mutation of single nucleotide variant

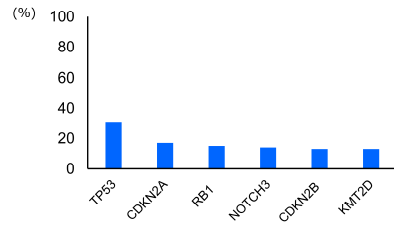


Figure2. The number of the patients with high Tumor mutational burden

